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Short Communication

The application of current lifetable methods to compare cystic fibrosis median survival internationally is limited

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Abstract

Background: Comparing international estimates of survival can be a useful way of highlighting differences in life expectancy between cystic fibrosis (CF) populations. In this study, we compared survival in two CF populations.
Methods: The current lifetable method takes age-specific mortality rates observed in a given year and applies them to a hypothetical population assuming those rates will remain the same in the future. This was used to compare median predicted survival in the United States (US) and the Republic of Ireland (RoI) (1986–2008). Median age at death among decedents was also examined.
Results: In both countries, median age at death was lower than median predicted survival. Successive increases in annual median predicted survival were not observed; rather an overall improvement was discerned over time. In the RoI, where absolute numbers of deaths were small, year-on-year fluctuations in age-specific mortality rates resulted in wide-ranging annual median predicted survival estimates.
Conclusion: Median age at death is not a good measure of CF survival. Though median predicted survival improved in each country over the study period, between-country comparison at a given time point may be misleading for rare disorders like CF. Longitudinal outcomes must be examined.

Keywords: Cystic fibrosis; Mortality; Survival analysis; Current lifetable; Registry

1. Introduction

Comparing international estimates of survival can be a useful way of highlighting differences in life expectancy between cystic fibrosis (CF) populations [1]. Yet such an undertaking is not straightforward; initial challenges include accessing data on age and vital status [2]. Two measures of survival are used in CF; median age at death and median predicted survival. Although both are interpreted as measures of survival, their meanings differ and this often leads to confusion. Median age at death is based on decedents in a CF population (mortality records are used in its calculation) and the duration of life remaining in those still alive is not a consideration. Median predicted survival estimation takes age-specific mortality rates observed in a calendar year and estimates life expectancy for a hypothetical population by assuming that current mortality rates validly estimate future rates and remain constant over the population's lifetime [3]. It has been used by the US CF Registry to monitor temporal trends in median predicted survival since 1986, as birth cohort follow-up has not yielded a median survival value (>50% of the cohort are alive to date).

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However, methods of estimating median predicted CF survival have not yet been standardised; estimates are often derived from different baselines (birth or one year of age) or collapsed into arbitrary age classes and/or time periods when populations are small [2,4–7]. The United Kingdom (UK) CF Trust recently overcame this challenge by applying the United States (US) CF Foundation (CFF) Patient Registry current lifetable methodology, thus directly comparing UK survival estimates with that of the US [8,9]. Median predicted survival estimates of 38.8 and 37.4 years were reported by the UK and US registries respectively for 2008 [10,11].

While large, long-established registries provide greater statistical power in survival analyses, national survival statistics are required by all countries to inform local service provision. The aim of this study was to directly compare CF survival estimates between the US and the Republic of Ireland (RoI) (1986–2008) using the CFF Patient Registry current lifetable methodology. UK median predicted survival estimates were available for 2007 and 2008 only, therefore our comparison focussed on the US and the RoI.

2. Methods

Annual median age at death and annual median predicted survival (and 95% CIs) were derived from the CFF Patient Registry, which in 2008 contained information on >25,000 patients attending CF care centres (representing 90% of all US CF patients). All deaths and death dates are confirmed by direct contact with the care centres.

By 2008, six years after initiation of the Cystic Fibrosis Registry of Ireland (CFRI) and following a stringent validation process to determine population ascertainment, 90% (n=1062) of the RoI CF population had registered. Study patients were identified through the CFRI or a listing of deaths compiled from three sources; records of registered deaths with CF as the underlying cause 1986–2008 provided by the Central Statistics Office, CF centre attendee deaths (2002–7), and CF patient association recorded deaths (1986–2007). Subjects on the CFRI not reported as deceased by 31st December 2008 were therefore presumed to be alive.

The CFF Patient Registry current lifetable method [10] was applied to the RoI data to calculate median predicted survival estimates from 1986 to 2008. To avoid bias introduced by assuming that all persons with CF (PWCF) were followed from birth, the observation period started with the date of diagnosis (a programme of newborn screening has not yet been introduced in the RoI). Potential for bias resulting from deaths occuring between diagnosis and CFRI enrolment was avoided by the utilisation of registered death records. Annual populations were defined from 1986 to 2008, each comprising PWCF diagnosed in the year of observation or the years preceding it. For decedents with a missing date of diagnosis we adopted an alternative entry date. For those who died before their first birthday, a missing date of diagnosis was taken to be the date of birth. Those dying after their first birthday with a missing date of diagnosis were stratified into two groupings; 1 to 24 years and ≥25 years. A missing date of diagnosis was set as the mean age at diagnosis of those patients with valid data in that group. The cut point of 25 years was necessitated by the age distribution of age at death in valid cases.

Median predicted survival was estimated for a hypothetical population of PWCF by applying the observed age-specific rates in that year. Cumulative survival was calculated at each age. Median predicted survival was derived as the age at which cumulative survival dropped below the 50% level. Ninety-five percent confidence intervals (CIs) were calculated as per the CFF methodology [10]. Patients who underwent a solid-organ transplantation are not excluded/censored [10]. Calculations were performed on the RoI data using SPSS (version 15, SPSS Inc.) and validated using the CFF's lifetable procedure programme in SAS (version 8.2, SAS Institute). Time trends in survival were examined using Pearson's correlation coefficient. Median predicted survival regression line slopes were compared according to Zar's method [12] using GraphPad Prism (version 5.03, GraphPad Software Inc.).

3. Results

In the RoI and the US respectively, 421 (average 18.3, range 7–31) and 8849 (average 384.7, range 329–459) deaths occurred between 1986 and 2008. In both countries median age at death increased between 1986 and 2008, but did not exceed 24 years in the RoI (26 in the US). Median age at death was lower than median predicted survival at each annual time point (Fig. 1, Table 1).

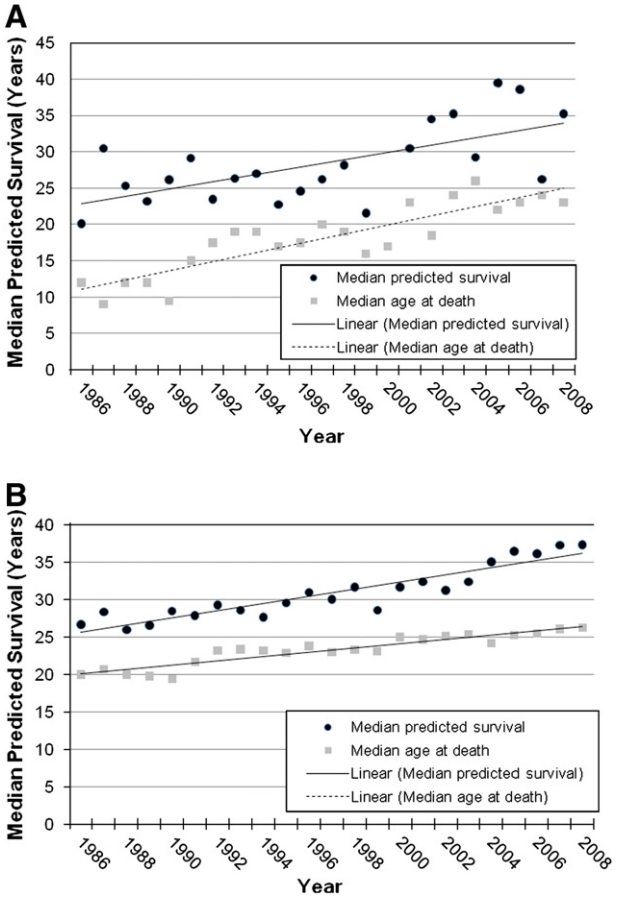

Fig. 1. Median age at death and current lifetable estimates of median predicted survival (in years) for the Republic of Ireland (A) and United States (B), 1986–2008.

Table 1
Number of deaths and median predicted survival for persons with cystic fibrosis (CF) in the Republic of Ireland and the United States.

	Republic of Ireland			United States		
Year	Number of CF deaths	Median predicted survival	(95% CI)	Number of CF deaths	Median predicted survival	(95% CI)
1986	20	20.1	(13.0, 34.4)	339	26.7	(25.3, 28.3)
1990	14	26.1	(10.7, na)	343	28.5	(26.5, 31.0)
1994	18	27.0	(17.0, 30.5)	411	27.7	(26.3, 29.7)
1998	25	28.2	(20.0, 32.4)	388	31.7	(29.5, 33.7)
2002	18	34.5	(21.7, na)	426	31.3	(29.7, 33.1)
2003	16	35.2	(24.9, na)	370	32.4	(30.3, 35.1)
2004	19	29.2	(26.2, na)	369	35.1	(33.0, 38.1)
2005	17	39.5	(25.7, na)	357	36.5	(33.7, 40.0)
2006	13	38.6	(33.8, na)	370	36.2	(33.6, 40.6)
2007	31	26.2	(19.1, 31.4)	397	37.3	(35.6, 39.2)
2008	21	35.2	(24.5, na)	420	37.4	(35.0, 40.1)

Na: not available due to small numbers of deaths.

Median predicted survival first exceeded thirty years in the US in 1996 and 2001 in the RoI.

Median predicted survival estimates fluctuated from year-to-year and fluctuations were more marked in the RoI ($r^2=0.42$) than in the US ($r^2=0.86$). The highest US median predicted survival (37.3 years) was recorded in 2007 following successive increases since 2002. In the RoI, median predicted survival estimates ranged from 26.2 to 39.5 years from 2000 onwards.

Median predicted survival regression lines showed that CF survival improved overall during the study period. The rate of improvement was similar in the US and the RoI as regression slopes did not differ significantly; slope point estimates of 0.48 (95% CI: 0.39, 0.57) and 0.5 (95% CI: 0.23, 0.79) were observed respectively.

4. Discussion

In this study, we identified an important limitation of comparing survival estimates for CF, a rare disease with an evolving decedent age profile when using a standardised current lifetable method to directly compare the US and the RoI median predicted survival estimates.

The first problem arising from using current lifetables to derive an annual median predicted survival estimate is that temporal fluctuations in annual age-specific mortality rates cannot be taken into account. The current lifetable technique takes age-specific mortality rates observed in a calendar year and estimates life expectancy by assuming that current mortality rates validly estimate future rates and remain constant over the population's lifetime [3]. However, CF survival in the RoI is improving overall, mirroring a pattern of increased life expectancy in the US and elsewhere in recent decades [6]. Survival has improved particularly in childhood, in the 2–15 year old age group [13,14].

While age-specific mortality rates used to derive current lifetable estimates of median predicted survival will vary from year-to-year in CF registries of all size, variability may be particularly marked in countries with small absolute numbers of deaths. Consequently, comparisons of survival estimates with international leaders at specific time points may be misleading. While US and RoI annual median predicted that survival was broadly similar, there were exceptions for example; in 2007 the US median predicted that survival estimate was 37.4 (95% CI: 35.7, 39.2 years) compared with 26.2 years (95% CI: 19.1, 31.4) in the RoI. An unusually large number of deaths, particularly in childhood, occurred in the RoI in that year (n=31) and was more than twice the number reported in the previous year (n=13). Yet, median predicted survival in the subsequent year (2008) was similar (37.4 and 35.2 years in the US and RoI respectively).

Previous comparisons of CF survival estimates have utilised national mortality statistics to calculate median age at death, in order to make inferences about survival [2]. Median age at death fluctuates with the age structure of the CF population, and will increase as greater proportions of PWCF reach adulthood. However, this statistic becomes less meaningful when the observed population's mortality rate is low. This became apparent when median age at death was shown to underestimate CF survival derived using the current lifetable method.

Using linear regression to examine temporal patterns, we found that median predicted survival improved at the same rate in both countries, but was slightly higher in the US. Registry selection bias is an important consideration for current lifetable analysis [1,6,15] as omission of unrecognised deceased PWCF can positively bias estimates, and may be one reason for the observed difference. In the RoI dataset, registry data with a high level of ascertainment was used together with registered death information. Also, CF services in the RoI are available free of charge, so the identification of the CF population may be easier.

5. Conclusion

Median age at death may not be a useful measure of survival as it provides a lower estimate than median predicted survival. Calculating median predicted survival can be a useful way for individual countries to monitor temporal trends in survival. However, comparison of median predicted survival between small and large CF registries at a given time point can be misleading because of instability in annual age-specific mortality rates. Analysis of longitudinal outcomes could provide better insights into survival trends.

Conflict of interest

None declared.

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